REMARKS

I. Status of the Claims

Claims 1-21 and 27-32 are withdrawn. Claims 22 and 24-26 are amended. Support for the amendments may be found, for example, at page 4, line 27 to page 5, line 10; page 8, lines 17-20; and page 9, lines 5-11. Claims 22 and 24-26 and 33-38 are pending.

No new matter is believed to have been added.

II. Claim Objection

The Examiner has objected to claim 22 because the claim included the language "from 01% to 40%." As the Examiner noted, this amount should read "from 0.1% to 40%." Applicants have amended the claim to recite the proper amount and request the objection be withdrawn.

III. Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claim 25 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement because it contains the language "ethylcellulose and its derivates." Applicants have amended claim 25 to remove the "and its derivates" language, and therefore, request that the §112, first paragraph rejection be withdrawn.

IV. Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 22-26 and 33-38 under 35 U.S.C. §112, second paragraph for allegedly being indefinite for failing to distinctly claim the subject matter the applicants regard as their invention. Applicants respectfully traverse the Examiner's rejection, but, in order to expedite prosecution, have amended claims 22 and 24 to clarify the that the active ingredient is present in the polymeric membrane coating. As the Examiner's rejection has been rendered moot by these amendments, Applicants request that the §112, second paragraph rejection be withdrawn.

The Examiner has rejected claim 24 under 35 U.S.C. §112, second paragraph for allegedly being indefinite for reciting the limitation, ". . . characterized by a modified release of the active ingredient." Applicants respectfully traverse this rejection. The term "modified

release" is a term of art, as can be seen, for example, by its specific use in *Remington*, which notes, "most *modified-release* delivery systems fall into the following four categories: 1. Delayed-release[;] 2. Extended-release[;] 3. Site-specific targeting[; and] 4. Receptor targeting" (emphasis added).[1] Further, the specification of the claimed invention supports this definition. For example, at page 9, line 8, it states, "[t]he modified release, *in particular delayed release*," and notes the modified release profiles in Examples 4, 8, and 10. As such, Applicant submit the skilled artisan would readily understand the meaning of the term "modified release". Therefore, Applicants respectfully request that the §112, second paragraph rejection based on use of the term "modified release" be withdrawn.

V. Rejection Under 35 U.S.C. §103(a)

The claims have been rejected over the combination of Thakur[2], Topiramate[3], MSDS[4], Skinner[5], and optionally Banakar[6], or over the combination of Powell[7], Santa Cruz[8], and optionally Banakar.

Applicants respectfully traverse these rejections and respectfully submit that the Examiner has failed to properly establish a *prima facie* case of obviousness.

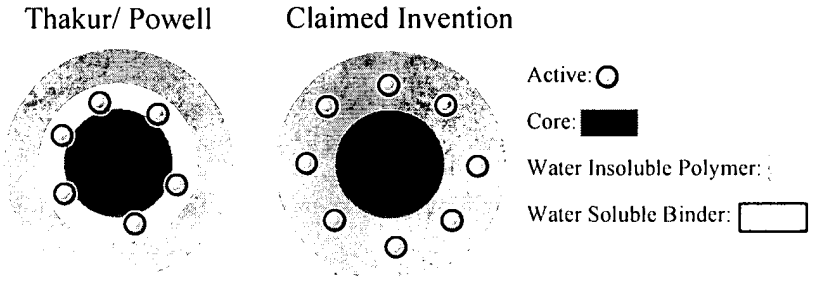
Applicants' claim 22 recites, *inter alia*, "[m]icrocapsules comprising . . . a core having an average particle size ranging from 50 to 1200 μm; and . . . a polymeric membrane coating said core . . . containing at least one water-soluble active ingredient homogeneously dispersed in said polymeric membrane coating in the form of solid particles." In essence, Applicants' invention requires: (1) at least one layer comprising the combination of an active ingredient *and* a water insoluble polymer, and (2) the active ingredient is dispersed homogeneously in the water insoluble polymer. These requirements are not found in any of the references cited by the Examiner.

Thakur and Powell disclose compositions where the active ingredient in a water-

[1] Remington, The Science and Practice of Pharmacy 21st Ed. 939-40 (2006).
[2] U.S. Publ. No. 2002/006456.
[3] http://chemicalland21.com/lifescience/phar/TOPIRAMATE.htm
[4] Material data safety sheet for cellulose acetate.
[5] G.W. Skinner *et al.*, Pharm. Tech. Report PTR-025 (2003).
[6] U.V. Banakar, 49 Drugs Pharm. Sci. 144 (1992).
[7] U.S. Patent No. 5,252,337.
[8] http://www.scbt.com/datasheet-200199.html.

soluble polymer or binder is coated onto a core particle. For example, Thakur describes "a particularly preferred embodiment of the process for preparing the sprinkle formulation, [wherein] a suspension of topiramate in a solution of povidone [*i.e., a water soluble polymer*] in purified water is sprayed onto sugar spheres" (emphasis added).[9] Similarly, Powell teaches, "[t]he calcium channel blocker is first loaded onto nonpareil seeds to form the core . . .[t]he calcium channel blocker is applied to the core from an aqueous solution or dispersion containing a binder of any water soluble polymer" (emphasis added).[10] Thus, both Thakur and Powell teach a quite different active ingredient containing layer – a mixture of the active ingredient with a water soluble polymer rather than the water insoluble polymer of the claimed invention.

In addition, both Thakur and Powell teach a water-insoluble polymer layer – which does not contain active ingredient -- deposited as a separate layer on top of the active ingredient containing layer. The resulting structure of the Thakur/Powell compositions can be seen in Figure 1 (below).



As noted in the figure above, in both Thakur and Powell, the core particle is coated with a water insoluble polymer layer ***on top of*** the active ingredient and water soluble binder/polymer layer. In contrast, the claimed invention has a single layer combining the water insoluble polymer and the active ingredient.

As noted above, the claimed invention requires a homogenous dispersion of the active ingredient in the polymeric membrane coating. Homogeneous is defined as "[p]ertaining to a

[9] *See, e.g.*, Thakur, U.S. Publ. No. 2002/0064563, ¶ [0037].
[10] Powell, U.S. Patent No. 5,252,337, col. 3, lines 43-44 and col. 3, lines 51-54.

substance having uniform composition or structure,"[11] and dispersion is defined as "[a] distribution of finely divided particles in a medium,"[12] the claimed invention requires that the active must be uniformly distributed in the polymeric membrane coating.

If the inner layer of the Thakur/Powell coating is considered a polymeric membrane coating, it differs from the composition of the claimed invention because it comprises a water soluble polymer rather than a water insoluble polymer. However, even if, *arguendo*, the Thakur/Powell two-layer coating is considered to constitute a single layer, the distribution of the active ingredient would not be homogeneous because they are concentrated in the inner layer, and are absent in the outer layer. Thus, Thakur and Powell both fail to teach a single layer comprising the combination of an active ingredient and a water insoluble polymer, and fail to teach an active ingredient distributed homogeneously within a polymeric membrabe coating.

The additional references cited by the Examiner fail to cure the deficiencies in Thakur and Powell. Banakar speaks only to particle size. Topiramate and Santa Cruz only describe the physical characteristics of the active compounds. MSDS only describes the physical properties and safety characteristics of cellulose acetate. And Skinner is directed to evaluating the properties of HPMC as a direct compression binder. None of these references teach a core coated with a layer comprising and active ingredient combined with a water insoluble polymer, or an active ingredient homogeneously dispersed in such a layer. Therefore, as the references individually fail to teach or suggest these limitations, the combined references also necessarily fail to all the limitations of the claimed invention. Accordingly, Applicants submit that the Examiner has failed to establish a case of *prima facie* obviousness for claim 22, and claims 24-26 and 33-38, which depend therefrom. Applicants therefore respectfully request that the rejection be withdrawn.

VI. Provisional Obviousness-Type Double Patenting Rejection

The Examiner has rejected the claims on the grounds of nonstatutory obviousness-type double patenting over various claims of copending U.S. Serial No. 10/521,598 (the '598

[11] Dictionary of Scientific and Technical Terms, 4th ed., McGraw-Hill (1989).
[12] *Id.*

application). The pending claims of the '598 application are directed to a drug containing particle coated with various polymeric layers. None of these polymeric layers expressly includes the active ingredient, and thus necessarily fail to disclose the claimed polymeric membrane coating comprising an active ingredient and a water insoluble polymer, wherein the active ingredient is homogeneously dispersed therein. Accordingly, the claims of the '598 application fail to support a case of *prima facie* obviousness, and thus fail to teach or suggest the claimed invention. Applicants respectfully request that this rejection be withdrawn.

VII. Obviousness Type Double Patenting Over Claims of US 5,296,236 and US 5,510,119

The claims of US 5,296,236 (the '236 patent) and US 5,510,119 (the '119 patent) are directed to microgranules containing a "pharmaceutical" (i.e., active ingredient), which are then over-coated with various polymeric layers. None of these polymeric layers includes the active ingredient (which is in the microgranule, i.e., core) of the dosage form. Thus, the claims of the '236 patent and the '119 both necessarily fail to disclose the claimed polymeric membrane coating comprising an active ingredient and a water insoluble polymer, wherein the active ingredient is homogeneously dispersed therein. Accordingly, the claims of the '236 patent and the '119 patent fail to support a case of *prima facie* obviousness, and thus fail to teach or suggest the claimed invention. Applicants respectfully request that this rejection be withdrawn.

In view of the foregoing, Applicants respectfully submit that no further impediments exist to the allowance of this application and, therefore, request an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. 1.136(a)(3).

Dated: 3/15/2010

Respectfully submitted,
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CHAPTER 47

Extended-Release and Targeted Drug Delivery Systems

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The goal of any drug delivery system is to provide a therapeutic amount of drug to a proper site in the body so that the desired drug concentration can be achieved promptly and then maintained. That is, the drug-delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of time. This idealized objective points to the two aspects most important to drug delivery, namely, *spatial placement* and *temporal delivery*. Spatial placement relates to targeting drugs to specific organs, tissues, cells, or even subcellular compartments; whereas temporal delivery refers to controlling the rate of drug delivery to the target site. An appropriately designed controlled drug delivery system can be a major advance toward solving these two problems. It is for this reason that the science and technology responsible for development of controlled drug delivery has been, and continues to be, the focus of a great deal of attention in both industrial and academic laboratories. The history of controlled delivery technology can be divided roughly into three time periods. From 1950 to 1970 is the period of extended drug release. A number of systems containing hydrophobic polymers and waxes were fabricated with drugs into dosage forms with the aim of maintaining drug levels and, hence, drug action for an extended period of time. However, a lack of understanding of anatomic and physiologic barriers impeded the development of efficient delivery systems. From 1970 to 1990, research mainly focused on determining the needs in controlled drug delivery and on understanding the barriers for various routes of administration. Zero-order release was emphasized in controlled drug delivery. Interest in drug targeting accelerated during this period as well. The rapid progress in biotechnology and molecular biology promoted drug delivery research in the 1980s and early 1990s. Post 1990, the modern era of controlled drug delivery technology, represents the period in which an attempt at drug optimization was emphasized. In the past two decades, considerable effort has been expended on developing novel polymeric carriers, biomacromolecule delivery systems, etc.[1] Currently, numerous products formulated for various routes of administration and claiming sustained or controlled drug delivery, exist on the market. The bulk of research has been directed toward oral dosage forms that satisfy the temporal aspect of drug delivery. In addition, some of the newer approaches under investigation may allow for spatial placement as well.

CONVENTIONAL DRUG THERAPY

To gain an appreciation for the value of controlled drug therapy, it is useful to review some fundamental aspects of conventional drug delivery. Consider single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the drug can produce a drug blood level versus time profile similar to that shown in Figure 47-1. The term *drug blood level* refers to the concentration of drug in blood or plasma, but the concentration in any tissue could be plotted on the ordinate. It can be seen from this figure that administration of a drug by either intravenous injection or an extravascular route (eg, orally, intramuscularly, or rectally) does not maintain drug blood levels within the therapeutic range for an extended period of time. The short duration of action is due to the inability of conventional dosage forms to control temporal delivery. If an attempt is made to maintain drug blood levels in the therapeutic range for longer periods by, for example, increasing the initial dose of an intravenous injection, as shown by the dotted line in Figure 47-1, toxic levels may be produced at early time points. Obviously, this approach is undesirable and unsuitable. An alternative approach is to administer the drug repetitively using a constant dosing interval, as in a multiple-dose therapy. This is shown in Figure 47-2 for the oral route. In this case the therapeutic drug blood level reached and the time required to reach that level depend on the dose and the dosing interval.

There are several potential problems inherent in multiple-dose therapy:

1. If the dosing interval is not appropriate for the biological half-life of the drug, large peaks and valleys in the drug blood level may result. For example, drugs with short half-lives require frequent dosing to maintain constant therapeutic levels.
2. The drug blood level may not be within the therapeutic range at sufficiently early time points, an important consideration for certain disease states.
3. Patient noncompliance with the multiple-dosing regimen can result in failure of this approach.

In many instances, potential problems associated with conventional drug therapy can be overcome. When this is the case, drugs given in conventional dosage forms by multiple dosing can produce the desired drug blood level for extended periods of time. Frequently, however, these problems are significant enough to make drug therapy with conventional dosage forms less desirable than modified-release drug therapy. This fact, coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling stimulus for development of controlled drug delivery systems.

MODIFIED-RELEASE DRUG THERAPY

Terminology

Currently, most modified-release delivery systems fall into the following four categories:

1. Delayed-release
2. Extended-release

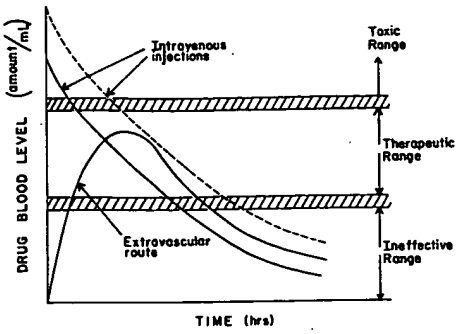

Figure 47-1. Typical drug blood level versus time profiles for intravenous injection or an extravascular route of administration.

3. Site-specific targeting
4. Receptor targeting

Delayed-release systems are either those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dosage form, or an enteric delayed release system. Examples of delayed-release systems include repeat-action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating.

Extended-release systems include any dosage form that maintains therapeutic blood or tissue levels of the drug for a prolonged period. If the system can provide some actual therapeutic control, whether this is temporal or spatial or both, of drug release in the body, it is considered a controlled delivery system. This explains why extended-release is not equivalent to controlled-release.

Site-specific and *receptor targeting* refer to targeting a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissue; for receptor release, the target is the particular drug receptor within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery requirement and are also considered controlled drug delivery systems.

Controlled drug delivery can be defined as delivery of the drug at a predetermined rate and/or to a location according to the needs of the body and disease states for a definite time period. A controlled delivery system must fulfill one or several of the following requirements[2]:

1. *Extend drug action at a predetermined rate* by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects that may be associated with a sawtooth kinetic pattern of conventional release.
2. *Localize drug action* by placing a controlled delivery system (usually rate-controlled) adjacent to or in a diseased tissue or organ.
3. *Target drug action* by using carriers or chemical derivatives to deliver a drug to a particular target cell type.
4. *Provide a physiologically/therapeutically based drug release system.* In other words, the amount and the rate of drug release are determined by the physiological/therapeutic needs of the body.

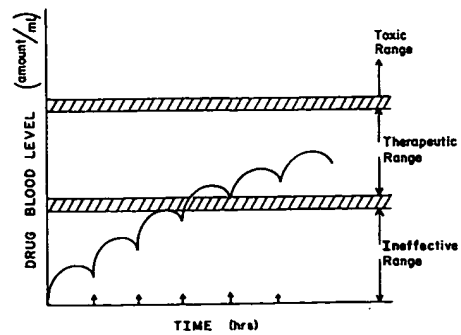

Figure 47-2. Typical drug blood level versus time profile following oral multiple-dose therapy.

Recently, a novel modification of drug delivery systems has emerged from the pharmaceutical industry. A *fast-dissolve drug delivery system* consists of a solid dosage form that dissolves or disintegrates in the oral cavity without the need of water or chewing. Among commercial products, fast dissolution or disintegration is achieved by forming an open matrix network containing the active ingredient (Zydis, *Eli Lilly*), by incorporating saliva-activated effervescent agents (OraSolv, *Cima*), or by using a mixture of a disintegrating agent and a swelling agent (Flashtab, *Prographarm*).[3]

Potential Advantages

All modified-release products share the common goal of improving drug therapy over that achieved with their conventional counterparts. There are several potential advantages of modified-release systems over conventional dosage forms, as shown in Table 47-1.

Patient compliance has been recognized as a necessary and important component in the success of all self-administered drug therapies. Minimizing or eliminating patient compliance is an obvious advantage of extended-release therapy. Because of the nature of its release kinetics, an extended-release system should be able to use less total drug over the time course of therapy than a conventional preparation. The advantages of this are a decrease or elimination of both local and systemic side effects, less potentiation or reduction in drug activity with chronic use, and minimization of drug accumulation in body tissues with chronic dosing.

The most important reason for modified-release drug therapy is improved efficiency in treatment (ie, optimized therapy). By obtaining constant or some other pattern of drug blood levels from an extended-release system, the desired therapeutic effect can be obtained promptly and maintained for a prolonged period of time. Reducing or eliminating fluctuations in the drug blood level allows better disease state management. In addition, the method by which extended release is achieved can improve the bioavailability of some drugs. For example, drugs susceptible to enzymatic inactivation or bacterial decomposition can be protected by encapsulation in polymeric systems suitable for extended release. For drugs that have a specific window for absorption, increased bioavailability can be achieved by localizing the extended-release delivery system in certain regions of the gastrointestinal tract. Improved efficiency in treatment also can take the form of a special therapeutic effect not possible with a conventional dosage form.

The last potential advantage listed in Table 47-1 (ie, economic savings) can be examined from two points of view. Although the initial unit cost of most extended-release delivery systems usually is greater than that of conventional dosage forms because of the special nature of these products, the average cost of treatment over an extended time period may be

Table 47-1. Potential Advantages of Modified-Release Drug Therapy

1. Avoid patient compliance problems
2. Employ less total drug
   a. Minimize or eliminate local side effects
   b. Minimize or eliminate systemic side effects
   c. Obtain less potentiation or reduction in drug activity with chronic use
   d. Minimize drug accumulation with chronic dosing
3. Improve efficiency in treatment
   a. Cure or control condition more promptly
   b. Improve control of condition (ie, reduce fluctuation in drug level)
   c. Improve bioavailability of some drugs
   d. Make use of special effects (eg, sustained-release aspirin for morning relief of arthritis by dosing before bedtime)
4. Economic savings

lower. Economic savings also may result from a decrease in nursing time/hospitalization, less lost work time, etc.

DRUG PROPERTIES RELEVANT TO EXTENDED-RELEASE FORMULATION

The design of extended-release delivery systems is subject to several variables of considerable importance. Among these are the route of drug administration, the type of delivery system, the disease being treated, the patient, the length of therapy, and the properties of the drug. Each of these variables is interrelated, which imposes additional constraints upon the design of the delivery system. Of particular interest to the scientist designing the system are the constraints imposed by the properties of the drug. It is these properties that have the greatest effect on the behavior of the drug in the delivery system and in the body. The properties of a drug are conveniently described as being either physicochemical or biological. Obviously, there is no clear-cut distinction between these two categories, since the biological properties of a drug are a function of its physicochemical properties. For this discussion, however, those attributes that can be determined from *in vitro* experiments will be considered physicochemical properties. Biological properties resulting from typical pharmacokinetic studies on the absorption, distribution, metabolism, and elimination (ADME) characteristics of a drug and from pharmacodynamic studies will be covered in the next section.

Among all the physicochemical properties, solubility and membrane permeability are recognized as fundamental parameters controlling the rate and extent of drug absorption. A *Biopharmaceutic Drug Classification,* proposed by Amidon et al,[4] defines four cases of oral therapeutic products based on these two attributes:

1. High solubility-high permeability drugs.
2. Low solubility-high permeability drugs.
3. High solubility-low permeability drugs.
4. Low solubility-low permeability drugs.

Solubility and permeability play an influential role in the performance of conventional products; their role is even greater in extended-release systems.

Aqueous Solubility and pKa

It is well known that for a drug to be absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and, hence, the driving force for diffusion across membranes. Dissolution rate is related to aqueous solubility, as shown by the *Noyes-Whitney equation* that, under sink conditions, is

$$dC/dt = k_D A C_s \qquad (1)$$

where dC/dt is the dissolution rate, k_D is the dissolution rate constant, A is the total surface area of the drug particles, and C_s is the aqueous saturation solubility of the drug. The dissolution rate is constant only if A remains constant, but the important point to note is that the initial rate is directly proportional to C_s. Therefore, the aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and usually suffer oral bioavailability problems.

The aqueous solubility of weak acids or bases is governed by the pKa of the compound and the pH of the medium. For a weak acid

$$S_t = S_0 (1 + Ka/[H^+]) = S_0 (1 + 10^{\,pH-pKa}) \qquad (2)$$

where S_t is the total solubility (both the ionized and unionized forms) of the weak acid, S_0 is the solubility of the unionized form, Ka is the acid dissociation constant, and $[H^+]$ is the hydrogen ion concentration in the medium. Similarly, for a weak base

$$S_t = S_0 (1 + [H^+]/Ka) = S_0 (1 + 10^{\,pKa-pH}) \qquad (3)$$

where S_t is the total solubility (both the conjugate acid and free-base forms) of the weak base, S_0 is the solubility of the free-base form, and Ka is the acid dissociation constant of the conjugate acid. Equations 2 and 3 predict that the total solubility of a weak acid or base with a given pK_a can be affected by the pH of the medium.

Considering the pH-partition hypothesis, the importance of Equations 2 and 3 relative to drug absorption is evident. The pH-partition hypothesis simply states that the unionized form of a drug will be absorbed preferentially, in a passive manner, through membranes. Since weakly acidic drugs exist primarily in the unionized form in the stomach (pH = 1 to 2), their absorption will be excellent in such an acidic environment. On the other hand, weakly basic drugs exist primarily in the ionized form (conjugate acid) at the same site, and their absorption will be poor. In the upper portion of the small intestine, the pH is more basic (pH = 5 to 7), and the reverse will be expected for weak acids and bases. The ratio of Equation 2 or 3 written for either the pH of the gastric or intestinal fluid and the pH of blood is indicative of the driving force for absorption based on pH gradient. For example, consider the ratio of the total solubility of aspirin in the blood and gastric fluid

$$R = (1 + 10^{\,pHb-pKa})/(1 + 10^{\,pHg-pKa}) \qquad (4)$$

where pH_b is the pH of blood (pH 7.4), pH_g is the pH of the gastric fluid (pH 2), and the pKa of aspirin is about 3.4. Substituting these values into Equation 4 gives a value for R of $10^{3.8}$, indicating that aspirin is readily absorbed within the stomach. The same calculation for intestinal pH (about 7) yields a ratio close to 1, indicating less driving force for aspirin absorption within the small intestine. Ideally, the release of an ionizable drug from an extended-release system should be programmed in accordance with the variation in pH of the different segments of the gastrointestinal tract so that the amount of preferentially absorbed forms, and thus the plasma level of the drug, will be approximately constant throughout the time course of drug action.

In general, extremes in aqueous solubility of a drug are undesirable for formulation into an extended-release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution-limited absorption and yield an inherently sustained blood level. In most instances, formulation of such a drug into an extended-release system may not provide considerable benefits over conventional dosage forms. Even if a poorly soluble drug were considered a candidate for formulation into an extended-release system, a constraint would be placed on the type of delivery system that could be used. For example, any system relying on diffusion of the drug through a polymer as the rate-limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is drug concentration in the polymer or solution, and this concentration would be low. For a drug with very high solubility and a rapid dissolution rate, it is often quite difficult to decrease its dissolution rate and slow its absorption. Preparing a slightly soluble form of a drug with normally high solubility is one possible method for producing extended-release dosage forms.

Partition Coefficient

Between the time when a drug is administered and when it is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid-like barriers. A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes (ie, its membrane permeability) is its apparent oil/water partition coefficient, defined as

$$K = C_O/C_W \qquad (5)$$

where C_O is the equilibrium concentration of all forms of the

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On the title pages: Aerial photograph of the Sinai Peninsula made by Gemini spacecraft. (NASA)

McGRAW-HILL DICTIONARY OF SCIENTIFIC AND TECHNICAL TERMS, Fourth Edition

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transmitter, receiver, or adapter used for homing aircraft or used by aircraft for homing purposes. { 'hōm·iŋ di,vīs }

homing guidance [ENG] A guidance system in which a missile directs itself to a target by means of a self-contained mechanism that reacts to a particular characteristic of the target. { 'hōm·iŋ ,gīd·əns }

homing range [NAV] The maximum distance from a target or homing beacon at which a homing device is effective. { 'hōm·iŋ ,rānj }

homing relay [ELEC] A stepping relay that returns to a specified starting position before each operating cycle. { 'hōm·iŋ ¦rē,lā }

homing station [NAV] A station at which a beacon emits signals that may be used for homing. { 'hōm·iŋ ,stā·shən }

homing system [NAV] The two sets of equipment, one on a vehicle and the other on the ground or shore, that act cooperatively to keep some navigational parameter constant in the homing process. { 'hōm·iŋ ,sis·təm }

homing torpedo [ORD] A torpedo having homing guidance, designed for homing on a surface vessel or a submerged submarine. { 'hōm·iŋ tȯr'pē·dō }

homing transponder [NAV] A small acoustic transponder used in navigation of a submersible vehicle, which can be carried by the vehicle and quickly dropped when an area of interest is reached; a single transponder and a dead reckoning system are used. { 'hōm·iŋ tranz'pän·dər }

Hominidae [VERT ZOO] A family of primates in the superfamily Hominoidea containing one living species, *Homo sapiens*. { hä'min·ə,dē }

Hominoidea [VERT ZOO] A superfamily of the order Primates comprising apes and humans. { hä·mə'nȯid·ē·ə }

homo- [ORG CHEM] **1.** Indicating the homolog of a compound differing in formula from the latter by an increase of one CH_2 group. **2.** Indicating a homopolymer made up of a single type of monomer, such as polyethylene from ethylene. **3.** Indicating that a skeletal atom has been added to a well-known structure. [SCI TECH] Prefix indicating the same or similar. { 'hō·mō }

Homo [VERT ZOO] The genus of human beings, including modern humans and many extinct species. { 'hō·mō }

Homobasidiomycetidae [MYCOL] A subclass of basidiomycetous fungi in which the basidium is not divided by cross walls. { ¦hä·mō·bə,sid·ē·ō,mī'sed·ə,dē }

homobront *See* isobront. { ¦häm·ə¦bränt }

homocentric [OPTICS] Pertaining to rays which have the same focal point, or which are parallel. Also known as stigmatic. { ,häm·ə'sen·trik }

homocercal [VERT ZOO] Pertaining to the caudal fin of certain fishes which has almost equal lobes, with the vertebral column terminating near the middle of the base. { ,häm·ə'sər·kəl }

homochlamydeous [BIOL] Having all members of the perianth similar or not differentiated into calyx or corolla. { ¦hä·mō·klə'mid·ē·əs }

homochromy [ZOO] A form of protective coloration whereby the individual blends into the background. { hə'mäk·rə·mē }

homocline [GEOL] Any rock unit in which the strata exhibit the same dip. { 'hä·mə,klīn }

homocyclic compound [ORG CHEM] A ring compound that has one type of atom in its structure; an example is benzene. { ¦hä·mə'sī·klik 'käm,paùnd }

homocysteine [BIOCHEM] $C_4H_9O_2NS$ An amino acid formed in animals by demethylation of methionine. { ¦hä·mə'sis·tēn }

homocystinuria [MED] A hereditary metabolic disorder in which homocysteine appears in the urine because cystathionine synthetase activity is absent; there is also malpositioning of the lens, and mental retardation. { ¦hä·mə,sist·ən'ùr·ē·ə }

homodesmic [CRYSTAL] Of a crystal, having atoms bonded in a single way. { ,hä·mə'dez·mik }

homodont [VERT ZOO] Having all teeth similar in form; characteristic of nonmammalian vertebrates. { 'hä·mə,dänt }

homodynamic [INV ZOO] Developing through continuous successive generations without a diapause; applied to insects. { ,hä·mə,dī'nam·ik }

homodyne reception [ELECTR] A system of radio reception for suppressed-carrier systems of radiotelephony, in which the receiver generates a voltage having the original carrier frequency and combines it with the incoming signal. Also known as zero-beat reception. { 'hä·mə,dīn ri'sep·shən }

homoecious [BIOL] Having one host for all stages of the life cycle. { hō'mē·shəs }

homoeomerous [BOT] Having algae distributed uniformly throughout the thallus of a lichen. { ¦hō·mē¦äm·ə·rəs }

Homo erectus [PALEON] A type of fossil human from the Pleistocene of Java and China representing a specialized side branch in human evolution. { 'hō·mō ə'rek·təs }

homoerotism [PSYCH] Sexual desire directed toward a member of the same sex; usually sublimated and not expressed. { ¦hō·mō'er·ə,tiz·əm }

homofermentative lactobacilli [MICROBIO] Bacteria that produce a single end product, lactic acid, from fermentation of carbohydrates. { ¦hō·mō·fər'men·tə·tiv ¦lak·tō·bə¦sil·ē }

homogametic sex [GEN] The sex of a species in which the paired sex chromosomes are of equal size and which therefore produces homogametes. { ¦hä·mō·gə¦med·ik 'seks }

homogamety [GEN] The production of homogametes by one sex of a species. { ¦hä·mō'ga·məd·ē }

homogamous [BIOL] Of or pertaining to homogamy. { hə'mäg·ə·məs }

homogamy [BIOL] Inbreeding due to isolation. [BOT] Condition of having all flowers alike. { hə'mäg·ə·mē }

homogenate [BIOL] A tissue that has been finely divided and mixed. { hə'mäj·ə·nət }

homogeneity [PHYS] Quality of a substance whose properties are independent of position. [STAT] Equality of the distribution functions of several populations. { ,hō·mə·jə'nē·əd·ē }

homogeneous [CHEM] Pertaining to a substance having uniform composition or structure. [MATH] Pertaining to a group of mathematical symbols of uniform dimensions or degree. [SCI TECH] Uniform in structure or composition. { ,hä·mə'jē·nē·əs }

homogeneous atmosphere [METEOROL] A hypothetical atmosphere in which the density is constant with height. { ,hä·mə'jē·nē·əs 'at·mə,sfir }

homogeneous catalysis [CHEM] Catalysis occurring within a single phase, usually a gas or liquid. { ,hä·mə'jē·nē·əs kə'tal·ə·səs }

homogeneous chemical reaction [CHEM] Chemical reaction system in which all constitutents (reactants and catalyst) are of the same phase. { ,hä·mə¦jē·nē·əs ¦kem·i·kəl rē'ak·shən }

homogeneous coordinates [MATH] To a point in the plane with cartesian coordinates (x,y) there corresponds the homogeneous coordinates (x_1,x_2,x_3), where $x_1/x_3 = x$, $x_2/x_3 = y$; any polynomial equation in cartesian coordinates becomes homogeneous if a change into these coordinates is made. { ,hä·mə'jē·nē·əs kō'ȯrd·ən·əts }

homogeneous differential equation [MATH] A differential equation where every scalar multiple of a solution is also a solution. { ,hä·mə'jē·nē·əs ,dif·ə'ren·chəl i,kwā·zhən }

homogeneous equation [MATH] An equation that can be rewritten into the form having zero on one side of the equal sign and a homogeneous function of all the variables on the other side. { ,hä·mə'jē·nē·əs i'kwā·zhən }

homogeneous function [MATH] A real function $f(x_1,x_2, \ldots,x_n)$ is homogeneous of degree r if $f(ax_1,ax_2, \ldots,ax_n) = a^r f(x_1,x_2, \ldots,x_n)$ for every real number a. { ,hä·mə'jē·nē·əs 'fəŋk·shən }

homogeneous integral equation [MATH] An integral equation where every scalar multiple of a solution is also a solution. { ,hä·mə'jē·nē·əs 'int·ə·grəl i,kwā·zhən }

homogeneous line-broadening [OPTICS] An increase beyond the natural linewidth of an absorption or emission line which results from a disturbance (such as collisions or lattice vibrations) that is the same for all the source emitters. { ¦hō·mə'jē·nē·əs 'līn ,brȯd·ən·iŋ }

homogeneous network [COMPUT SCI] A computer network consisting of fairly similar computers from a single manufacturer. { ¦hō·mə'jē·nē·əs 'net,wərk }

homogeneous polynomial [MATH] A polynomial all of whose terms have the same total degree; equivalently it is a homogenous function of the variables involved. { ,hä·mə'jē·nē·əs ,päl·ə'nō·mē·əl }

homogeneous radiation [PHYS] Radiation having an extremely narrow band of frequencies, or a beam of monoener-

which uses magnetic disks as its primary on-line storage. { ¦disk ¦āp·ə,rād·iŋ ,sis·təm }

disk pack [COMPUT SCI] A set of magnetic disks that can be removed from a disk drive as a unit. { 'disk ,pak }

disk plow [AGR] A plow consisting of a number of disk blades attached to one axle or gang bolt; used for rapid, shallow plowing. { 'disk ,plaù }

disk population [ASTRON] The older Population I stars such as the sun. { 'disk ,päp·yə'lā·shən }

disk recording [ENG ACOUS] **1.** The process of inscribing suitably transformed acoustical or electrical signals on a phonograph record. **2.** *See* phonograph record. { ¦disk ri'kȯrd·iŋ }

disk sander [MECH ENG] A machine that uses a circular disk coated with abrasive to smooth or shape surfaces. { 'disk ,sand·ər }

disk-seal tube [ELECTR] An electron tube having disk-shaped electrodes arranged in closely spaced parallel layers, to give low interelectrode capacitance along with high power output, up to 2500 megahertz. Also known as lighthouse tube; megatron. { 'disk ,sēl ,tüb }

disk signal [CIV ENG] Automatic block signal with colored disks that indicate train movements. { ¦disk ¦sig·nəl }

disk spring [MECH ENG] A mechanical spring that consists of a disk or washer supported by one force (distributed by a suitable chuck or holder) at the periphery and by an opposing force on the center or hub of the disk. { 'disk ,spriŋ }

disk storage [ELECTR] An external computer storage device consisting of one or more disks spaced on a common shaft, and magnetic heads mounted on arms that reach between the disks to read and record information on them. Also known as disk memory; magnetic disk storage. { ¦disk ¦stȯr·ij }

disk telescope [OPTICS] A telescope designed for observations of the brilliant solar disk; examples are the tower telescope and the horizontal float telescope. { ¦disk 'tel·ə,skōp }

disk thermistor [ELECTR] A thermistor which is produced by pressing and sintering an oxide binder mixture into a disk, 0.2–0.6 inch (5–15 millimeters) in diameter and 0.04–0.5 inch (1.0–13 millimeters) thick, coating the major surfaces with conducting material, and attaching leads. { ¦disk thər'mis·tər }

disk unit *See* disk drive. { 'disk ,yü·nət }

disk-wall packer [PETRO ENG] A disklike seal between the outside of the well tubing and the inside of the well casing; used to prevent fluid movement from the pressure differential above and below the sealing point. { 'disk ,wȯl ,pak·ər }

disk wheel [DES ENG] A wheel in which a solid metal disk, rather than separate spokes, joins the hub to the rim. { 'disk ,wēl }

dislocation [CRYSTAL] A defect occurring along certain lines in the crystal structure and present as a closed ring or a line anchored at its ends to other dislocations, grain boundaries, the surface, or other structural feature. Also known as line defect. [GEOL] Relative movement of rock on opposite sides of a fault. Also known as displacement. [MED] Displacement of one or more bones of a joint. { ,dis·lō'kā·shən }

dislocation breccia *See* fault breccia. { ,dis·lō'kā·shən 'brech·ə }

dismicrite [GEOL] Fine-grained limestone of obscure origin, resembling micrite but containing sparry calcite bodies. { diz'mī,krīt }

dismount [ORD] To remove a weapon or piece of equipment from its setting, mount, or carriage. { dis'maünt }

disodium hydrogen phosphate *See* disodium phosphate. { dī'sōd·ē·əm 'hī·drə·jən 'fās,fāt }

disodium methylarsonate [ORG CHEM] $CH_3AsO(ONa)_2$ A colorless, hygroscopic, crystalline solid; soluble in water and methanol; used in pharmaceuticals and as a herbicide. Abbreviated DMA. { dī'sōd·ē·əm ¦meth·əl'ärs·ən,āt }

disodium phosphate [INORG CHEM] Na_2HPO_4 Transparent crystals, soluble in water; used in the textile processing and other industries to control pH in the range 4–9, as an additive in processed cheese to maintain spreadability, and as a laxative and antacid. Also known as disodium hydrogen phosphate. { dī'sōd·ē·əm 'fās,fāt }

disodium tartrate *See* sodium tartrate. { dī'sōd·ē·əm 'tär,trāt }

disomaty [CYTOL] Duplication of chromosomes unaccompanied by nuclear division. { dī'sō·məd·ē }

Disomidae [INV ZOO] A family of spioniform annelid worms belonging to the Sedentaria. { də'säm·ə,dē }

disophenol [PHARM] $I_2C_6H_2(NO_2)OH$ Light yellow, feathery crystals with a melting point of 157°C; soluble in alcohol; used as an antihelminthic drug in animals. { də'sä·fə,nōl }

disorder [CRYSTAL] Departures from regularity in the occupation of lattice sites in a crystal containing more than one element. { dis'ȯrd·ər }

disordered crystalline alloy [SOLID STATE] A mixture of two elements in which the atoms of the mixture are found at more or less random positions on a crystal lattice. { dis'ȯrd·ərd ¦krist·əl·ən 'al,ȯi }

disorientation [MED] Mental confusion as to one's normal relationship to his or her environment, especially time, place, and people; associated with organic brain disorders. { dis,ȯr·ē·ən'tā·shən }

dispatching [COMPUT SCI] The control of priorities in a queue of requests in a multiprogramming or multitasking environment. { dis'pach·iŋ }

dispatching priority [COMPUT SCI] In a multiprogramming or multitasking environment, the priority assigned to an active (non–real time, nonforeground) task. { dis'pach·iŋ prī,är·əd·ē }

dispenser [ENG] Device that automatically dispenses radar chaff from an aircraft. { də'spen·sər }

dispenser cathode [ELECTR] An electron tube cathode having provisions for continuously replacing evaporated electron-emitting material. { də'spen·sər ,kath,ōd }

dispermy [PHYSIO] Entrance of two spermatozoa into an ovum. { 'dī,spər·mē }

dispersal [CIV ENG] The practice of building or establishing industrial plants, government offices, or the like, in separated areas, to reduce vulnerability to enemy attack. [ORD] The spreading out of equipment, supplies, or personnel, especially for protection against enemy action. { də'spər·səl }

dispersal pattern [GEOCHEM] Distribution pattern of metals in soil, rock, water, or vegetation. { də'spər·səl ,pad·ərn }

disperse [COMPUT SCI] A data-processing operation in which grouped input items are distributed among a larger number of groups in the output. { də'spərs }

dispersed elements [GEOCHEM] Elements which form few or no independent minerals but are present as minor ingredients in minerals of abundant elements. { də'spərst 'el·ə·mənts }

dispersed gas injection [PETRO ENG] Gas-injection pressure maintenance of an oil reservoir in which the injection wells are arranged geometrically to distribute the gas uniformly throughout the oil-productive portions of the reservoir. { də'spərst 'gas in,jek·shən }

disperse dye [MATER] A very slightly water-soluble, colored material for use on cellulose acetate and other synthetic fibers; color is transferred to the fiber as extremely finely divided particles, resulting in a solution of the dye in the solid fiber. { də'spərs ,dī }

disperse phase [CHEM] The phase of a disperse system consisting of particles or droplets of one substance distributed through another system. Also known as discontinuous phase; internal phase. { də'spərs ,fāz }

disperser [MATER] Material added to solid-in-liquid or liquid-in-liquid suspensions to separate the individual suspended particles; used in pigment grinding and dye dispersion. Also known as dispersing agent; emulsifier; emulsifying agent. { də'spər·sər }

disperse system [CHEM] A two-phase system consisting of a dispersion medium and a disperse phase. { də'spərs ,sis·təm }

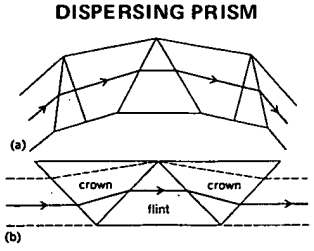
dispersible inhibitor [CHEM] An additive that can be dispersed in a liquid with only moderate agitation to retard undesirable chemical action. { di'spər·sə·bəl in'hib·əd·ər }

dispersing agent *See* disperser. { də'spərs·iŋ ,ā·jənt }

dispersing prism [OPTICS] An optical prism which deviates light of different wavelengths by different amounts and can therefore be used to separate white light into its monochromatic parts. { də'spərs·iŋ ,priz·əm }

dispersion [AERO ENG] Deviation from a prescribed flight path; specifically, circular dispersion especially as applied to missiles. [ASTRON] The frequency dependence of the retardation of radio waves (such as those emitted by a pulsar) when they pass through an ionized gas. [CHEM] A distribution of finely divided particles in a medium. [COMMUN] The entropy of the output of a communications channel when the input is known. [ELECTROMAG] Scattering of microwave radiation

DISPERSING PRISM



Two types of dispersing prisms. *(a)* Rayleigh prism system. *(b)* Amici direct-vision system consisting of flint-glass prism and two crown-glass prisms.

by an obstruction. [MINERAL] In optical mineralogy, the constant optical values at different positions on the spectrum. [PHYS] **1.** The separation of a complex of electromagnetic or sound waves into its various frequency components. **2.** Quantitatively, the rate of change of refractive index with wavelength or frequency at a given wavelength or frequency. **3.** The rate of change of deviation with wavelength or frequency. **4.** In general, any process separating radiation into components having different frequencies, energies, velocities, or other characteristics, such as the sorting of electrons according to velocity in a magnetic field. { də'spər·zhən }

dispersion equation *See* dispersion formula. { də'spər·zhən i'kwā·zhən }

dispersion error [ORD] Chance variation in a series of shots even though firing conditions are kept as constant as possible. { də'spər·zhən ˌer·ər }

dispersion force [PHYS CHEM] The force of attraction that exists between molecules that have no permanent dipole. { də'spər·zhən ˌfōrs }

dispersion formula [PHYS] Any formula which gives the refractive index as a function of wavelength of electromagnetic radiation. Also known as dispersion equation. { də'spər·zhən ˌfōr·myə·lə }

dispersion fuel [NUCLEO] A fuel mixture consisting of a nuclear fuel dispersed in a nonfissionable matrix. { də'spər·zhən ˌfyül }

dispersion ladder [ORD] Table showing the probable distribution of a succession of shots made with the same firing data; specifically, a diagram made up of eight zones, showing the percentage of shots which may be expected to fall within each zone, based on direction (deflection) or range. { də'spər·zhən ˌlad·ər }.

dispersion measure [ASTRON] A quantity that describes the dispersion of a radio signal, proportional to the product of the density of interstellar electrons and the distance to the source. { də'spər·zhən ˌmezh·ər }

dispersion medium *See* continuous phase. { də'spər·zhən ˌmēd·ē·əm }

dispersion mill [MECH ENG] Size-reduction apparatus that disrupts clusters or agglomerates of solids, rather than breaking down individual particles; used for paint pigments, food products, and cosmetics. { də'spər·zhən ˌmil }

dispersion of a random variable [STAT] The spread of a random variable's distribution about its mean. { də'spər·zhən əv ə ˈran·dəm 'ver·ē·ə·bəl }

dispersion pattern [ORD] The distribution of a series of shots by using coordinate settings as nearly identical as possible. { də'spər·zhən ˌpad·ərn }

dispersion relation [NUC PHYS] A relation between the cross section for a given effect and the de Broglie wavelength of the incident particle, which is similar to a classical dispersion formula. [PHYS] An integral formula relating the real and imaginary parts of some function of frequency or energy, such as a refractive index or scattering amplitude, based on the causality principle and the Cauchy integral formula. [PL PHYS] A relation between the radian frequency and the wave vector of a wave motion or instability in a plasma. { də'spər·zhən riˌlā·shən }

dispersion zone [ORD] The area over which shots scatter when fired with the same sight setting. { də'spər·zhən ˌzōn }

dispersive line [ELECTROMAG] A delay line that delays each frequency a different length of time. { də'spər·siv 'līn }

dispersive medium [ELECTROMAG] A medium in which the phase velocity of an electromagnetic wave is a function of frequency. { də'spər·siv 'mē·dē·əm }

dispersive power [OPTICS] A measure of the power of a medium to separate different colors of light, equal to $(n_2 - n_1)/(n - 1)$, where n_1 and n_2 are the indices of refraction at two specified widely differing wavelengths, and n is the index of refraction for the average of these wavelengths, or for the D line of sodium. { də'spər·siv ˌpaù·ər }

dispersoid [CHEM] Matter in a form produced by a disperse system. { də'spərˌsȯid }

disphenoid [CRYSTAL] **1.** A crystal form with four similar triangular faces combined in a wedge shape; can be tetragonal or orthorhombic. **2.** A crystal form with eight scalene triangles combined in pairs. { dīˈsfēˌnȯid }

displaced ore body [GEOL] An ore body which has been subjected to displacement or disruption after its initial deposition. { dis'plāst 'ȯr ˌbäd·ē }

displacement [CHEM] A chemical reaction in which an atom, radical, or molecule displaces and sets free an element of a compound. [COMPUT SCI] The number of character positions or memory locations from some point of reference to a specified character or data item. Also known as offset. [ELEC] *See* electric displacement. [FL MECH] **1.** The weight of fluid which is displaced by a floating body, equal to the weight of the body and its contents; the displacement of a ship is generally measured in long tons (1 long ton = 2240 pounds). **2.** The volume of fluid which is displaced by a floating body. [GEOL] *See* dislocation. [MECH] **1.** The linear distance from the initial to the final position of an object moved from one place to another, regardless of the length of path followed. **2.** The distance of an oscillating particle from its equilibrium position. [MECH ENG] The volume swept out in one stroke by a piston moving in a cylinder as for an engine, pump, or compressor. { dis'plās·mənt }

displacement angle [ELEC] The change in the phase of an alternator's terminal voltage when a load is applied. { dis'plās·mənt ˌaŋ·gəl }

displacement boat [NAV ARCH] Any ship or boat which travels immersed and operates at relatively lower speeds than craft, such as hydroplanes, which plane on the surface of the water at high speed. { dis'plās·mənt ˌbōt }

displacement chromatography [ANALY CHEM] Variation of column-development or elution chromatography in which the solvent is sorbed more strongly than the sample components; the freed sample migrates down the column, pushed by the solvent. { dis'plās·mənt ˌkrō·mə'täg·rə·fē }

displacement compressor [MECH ENG] A type of compressor that depends on displacement of a volume of air by a piston moving in a cylinder. { dis'plās·mənt kəmˌpres·ər }

displacement current [ELECTROMAG] The rate of change of the electric displacement vector, which must be added to the current density to extend Ampère's law to the case of time-varying fields (meter-kilogram-second units). Also known as Maxwell's displacement current. { dis'plās·mənt ˌkə·rənt }

displacement curve [NAV ARCH] A graph of the displacement of a vessel versus its draft; it is a curve of form. { dis'plās·mənt ˌkərv }

displacement efficiency [PETRO ENG] In a gas condensate reservoir, the proportion (by volume) of wet hydrocarbons swept out of pores during dry-gas cycling. { dis'plās·mənt ə'fish·ən·sē }

displacement engine *See* piston engine. { dis'plās·mənt ˌen·jən }

displacement fluid [MATER] A fluid material, usually drilling mud or salt water, that is pumped into a well after the cement to force the cement out of the casing and into the annulus. { dis'plās·mənt ˌflü·əd }

displacement gyroscope [ENG] A gyroscope that senses, measures, and transmits angular displacement data. { dis'plās·mənt 'jī·rəˌskōp }

displacement law *See* radioactive displacement law; Wien's displacement law. { dis'plās·mənt ˌlȯ }

displacement length coefficient [NAV ARCH] The displacement, in tons of sea water, of a ship divided by the length over 100 cubed. { dis'plās·mənt ˌleŋkth ˌkō·i'fish·ənt }

displacement manometer [ENG] A differential manometer which indicates the pressure difference across a solid or liquid partition which can be displaced against a restoring force. { dis'plās·mənt mə'näm·əd·ər }

displacement meter [ENG] A water meter that measures water flow quantitatively by recording the number of times a vessel of known capacity is filled and emptied. { dis'plās·mənt ˌmēd·ər }

displacement pump [MECH ENG] A pump that develops its action through the alternate filling and emptying of an enclosed volume as in a piston-cylinder construction. { dis'plās·mənt ˌpəmp }

displacement rate [PETRO ENG] In oil well cementing, the speed at which a given volume of cement slurry or mud is pumped down the borehole. { dis'plās·mənt ˌrāt }

displacement series [CHEM] The elements in decreasing order of their negative potentials. Also known as constant series; electromotive series; Volta series. { dis'plās·mənt ˌsir·ēz }